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A New Star is Born!

Dear reader,

Throughout history, the spread of knowledge in general and science in particular has primarily been achieved through publishing: traditionally it was through pen and paper, and now has evolved to different new audio and visual technologies. The recent advent of Internet has made this possibility even more attainable.

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minaret for mainstream advances in science, engineering, technology, arts and social sciences in both the advanced nations and the developing ones. It will promote collaboration between all scientists, and try to inseminate the nucleus of south-north scientific dialogue.

Science is universal and its message can be used for both related problems or in cross-disciplinary advances. Advanced research in genetic engineering may benefit local problems such as drought, and drought researchers can benefit other scientists. After all, we all learn from each other, but first they have to meet. This is one place where they can just do that.

Other niches may be explored by this new journal, such as literature reviews by research students and academics. This is due to the fact that most PhD students write comprehensive introductions for their subject but they to publish it; now they can.

In this way this publication links in a sense different niches and further allows scientific exchange between advanced scientific hubs such as the western world and the developing countries (the Arab world).

In achieving all this, the Journal will have strict and unique peer reviewing approach, that allow complete anonymity for both authors and reviewers. Publications will incur no or little cost for authors or readers, and more recognition to reviewers. This Open access publication should be viewed as a new breed of Journal publication. This journal is multidisciplinary journal targeted to all disciplines and as already explained is another product of IBScientific group (IBS). IBS was started by Algerian student researchers and have had received a huge support from Algerian scientists and academics and is well linked to other scientists. This publication is clear evidence that Algerian science need to be collaborative and see itself in a wider context of the worldwide scientific community. First, we introduce the Algerian day of science, the day of launching this publication.

16th of April 2006 is the Algerian day of science in commemoration of sheikh Abdelhamid Ibn Badis achievements, as he is viewed

as the leader of science reform in Algeria in different disciplines. He was a scholar and a scientist of wide acceptance for other faiths, and beliefs. He wanted to promoted scientific and academic studies and is an inspiration to all of us, he taught generations of scientists, engineers, historians, and philosophers that had universal impact such as Malek ben Nabi. This journal is published on this day, so we can always remember his quest for disseminating knowledge to the whole world, learning from them, and communicating with them.

Join us for this trip of discovery, and we will provide publication opportunities, an environment for collaboration, and critical thinking.

I thank everybody who made this project get this far, from the small well done to the technical help, not to forget both the positive and negative criticism. To you all thank you, and WELL DONE.

This project's achievement and measure is measured by your response.

I am just wondering what will be the next response...

Yours,

Abdelkader ESSAFI
IBS President and Editor-in-Chief
On behalf of the IBScientific team

C++ing Through The Bricks

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In the realm of software engineering, writing large programs could lead to a recipe of chaos. Other issues are also brought to the surface when considering extensibility, backward compatibility and debugging time and complexity. Therefore, it is often emphasised, sometimes even enforced, within software firms that programs should adhere to some programming style guidelines. A new programming approach has thus emerged with this idea in mind known as 'Object-Oriented'. It encompasses 'Inheritance' and other traits which provide a powerful and natural mechanism for organising and structuring software programs. This new style of programming has long suffered from drawbacks such as limited size and slow execution speed but the current advances in computer chips and compiler design have rendered these less noticeable.

The concept of object-oriented programming is finding more echoes from other engineering disciplines. Computational mechanical modelling is rapidly moving in this direction, for instance, to simulate structures and mechanical objects. In linear problems, Finite Element Methods dominate the scene with

regards to space discretisation. Traditionally, finite element software are written in procedural languages (such as FORTRAN and C) in which even the simplest codes can be hard to understand, and hence to re-use successfully by users.

In this inaugural issue of IBS Journal of Science, The authors, Belgasmia and Guenfoud, show in their article [1] the significant advantages of incorporating Object-Oriented approaches, as an alternative to procedural approaches, to finite element code development, in particular making the codes more usable, compact, and robust. These benefits are

established through the example a new C++ implementation of an isotropic and orthotropic plate formulation, using the powerful concepts of object, encapsulation, class, inheritance, and polymorphism. Adding this new piece to the jigsaw puzzle also highlights the extensibility of the code. Finally, a numerical example is proposed for the thirsty to drink!

[1] Belgasmia, M., and Guenfoud, M. (2006). Object Oriented Finite Element Formulation and Implementation of an Isotropic and Orthotropic Plate Element for Static Analysis. IBS Journal of Science, 1 (1), 8-14.

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27 Years of p53... Any More News?

Preview by:
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One of the current models for tumorigenesis suggests the accumulation of genetic alterations in pathways, which regulate cell proliferation, differentiation and cell death; as the driving force for neoplastic transformation. Mutations that underlie the tumorigenic process are believed to occur in three categories of genes: tumour suppressor genes, oncogenes, and stability genes. Tumour suppressors are particularly important because, as their name suggests, they fine-tune the homeostatic balance between cell growth and cell death. Indeed, tumour suppressor genes are commonly mutated in various cancer-predisposing inherited syndromes. Examples of the

classical tumour suppressors include adenomatous polyposis coli (APC), retinoblastoma (Rb) and p53. The multifunctional tumour suppressor p53 is critical for the cellular response to stress signals, and an important mediator of cell cycle arrest and programmed cell death, apoptosis. Not surprisingly, p53 is mutated in over 50% of human cancers; therefore therapeutic approaches aiming to restore p53 function in tumours could prove very effective.

In the current issue of IBS Journal of science, Saadi [2], highlights the crucial role of p53 in maintaining cellular and genetic integrity in response to stress conditions and discusses the therapeutic value of restoring p53 function in tumours. The author presents the four different modes for re-establishing an intact and functional p53 pathway. These include: p53 gene-replacement therapy, non-genotoxic stimulation of endogenous wild-type p53 and correction of both mRNA and protein products of mutant p53 genes. The author evaluates

each one of the four approaches in the light of some previous and ongoing studies. While the promises of gene replacement therapy for p53 are fading away, the potential of the other strategies awaits further elucidation.

The author also emphasises on the complexity of the p53 pathway, thus urges for the requirement of more understanding of the p53 pathway in normal and tumour cells. Additionally, the author proposes further investigations into the p53 pathway and its restoration strategies in cancer stem cells.

This unique perspective on p53 is highly valuable for the development of therapeutic methods targeting the causative and tumourigenic potential of p53 deregulation.

[2] Saadi, A. (2006). **Placing p53 Back on the Track... the Survival Track?** IBS Journal of Science, 1 (1), 16-23.

Object Oriented Finite Element Formulation and Implementation of an Isotropic and Orthotropic Plate Element for Static Analysis

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ABSTRACT

This article shows, through the example of the addition of a plate element to freeware FEM-Object, an Object-Oriented (C++) finite element program, how Object-Oriented approaches, as opposed to procedural approaches, make finite element codes more compact, more modular and versatile but mainly more easily expandable.

The fundamental traits of Object-Oriented programming are first briefly reviewed, and it is shown how such an approach simplifies the coding process. Then, the isotropic and orthotropic plate formulations used are given and the discretised equations developed. Finally, the necessary additions to the FEM-Object code are reviewed. Numerical examples using the newly created Plate element are shown.

KEYWORDS: finite element, Object-Oriented approach, plate element, isotropic, orthotropic, class inheritance.

1. INTRODUCTION

In the last decades, the finite element method has gained a large acceptance as a general tool for modelling and simulating physical systems. It has become, in fact, the most widely used technique applicable in fields such as solid mechanics, fluid mechanics, electromagnetism and so on. In recent years, easy maintenance, extensibility and flexibility of the finite element code, encouraged many researchers to change from procedural to Object-Oriented programming in order to make the finite element software more flexible.

The Object-Oriented programming approach appeared in the seventies and found its first convivial concretisation with the Small-Talk language at the beginning of the eighties. Applications in the finite element field appeared around 1990 (Zimmermann et al. 1992; Dubois-pélerin et al., 1992), and since then its use has spread. Object-Oriented approaches yield more modular programs than the standard procedural approach.

In this article, an Object-Oriented approach of the finite element method for the study of bending of isotropic and orthotropic plates in statics is presented as an extension of Freeware FEMObject (at <http://www.Zace.com/affemobj.html>).

The paper is organized as follows. In Section 2, it is shown how Ob-

ject-Oriented programming features, through the concept of Object, Class, Inheritance and Polymorphism, make it possible to overcome the limits inherited from procedural approaches. Section 3 deals with plate theory. Displacement and strain approximations are described, the equations of motion developed, the basics behind Mindlin-Reissner plate theory are recalled, and stiffness matrices for this formulation are developed. Section 4 is concerned with the addition of the aforementioned plate element into the FEMObject code described elsewhere (Commend and Zimmermann 2001). Object-Oriented programming is shown to easily accommodate the addition of a plate class, thus demonstrating code extensibility. Finally, Section 5 presents numerical results for isotropic and orthotropic thin plates and conclusions are given in Section 6.

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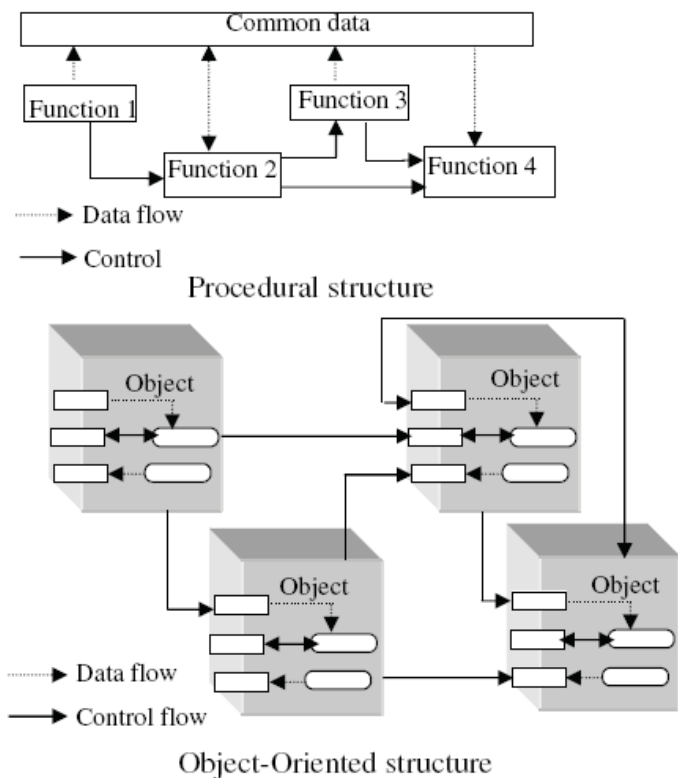


Figure 2.1: Different types of programming methods

2. OBJECT-ORIENTED PROGRAMMING

Procedural programming tends to show its limits especially for large finite-element programs, which contain hundreds of thousands of lines of code.

Such procedural programs are generally written in FORTRAN. This code contains a significant number of data structures which are accessible throughout the program, creating a loss of flexibility. It thus becomes difficult to modify the existing code and extend it to new uses. Loss of flexibility shows up in different manners:

- detailed knowledge of the program is required to work on a small part of the code,
- the re-use of the code is difficult,
- a small change in the data structures can influence the whole system,
- many interdependences between the components of the design are dissimulated and difficult to establish,
- the integrity of the data structures is not protected.

2.1. Review of Object-Oriented programming

The main concept of object-oriented programming (Delannoy, 2002; Jamsa and Klander, 1999; Dubois-p  lerin, 1993; and Mackie, 2001) is the abstraction, which leads to the faithful representation of the entities of the real physical world through the concept of object.

While Object-Oriented programming is intensively employed for

graphical applications, where the concept of "object" appears naturally, its use for scientific computation is still limited and industrial software is still generally written in FORTRAN, using procedural programming. Object-Oriented programming is based on the concepts of Object, Class, Inheritance, Polymorphism and Encapsulation. The difference between an Object-Oriented and a procedural implementation is shown in Figure 2.1.

An object is characterized by its identity, state and behaviour. The identity distinguishes an object from another. The state of an object is characterized by the current values of its attributes. The behaviour shows the action of the object under its own control and how it behaves with the external requests (see Figure 2.2).

The behaviour of the object is implemented through a set of operations working on its own attributes that are called methods. Methods and the data are encapsulated in the same enclosure (object), and they interact with the external world through an interface (see Figure 2.3).

Communication by means of messages requires the simplification of the destination object to which the request is addressed, and an indication of the method to be carried out.

The key advantages related to the use of objects are:

- Ease of comprehension and re-use of the code.
- Improvement in reliability, through encapsulation
- Increased abstraction and masking of information.

A class is an abstract data structure corresponding to objects sharing the same properties, attributes, and methods. The class specifies its own attributes and the methods are then able to operate on these attributes. From classes we instantiate objects which we activate by means of messages. The message activates the action, but the de-

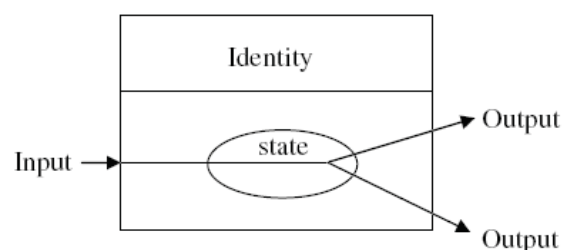


Figure 2.2: Behaviour and state of the object

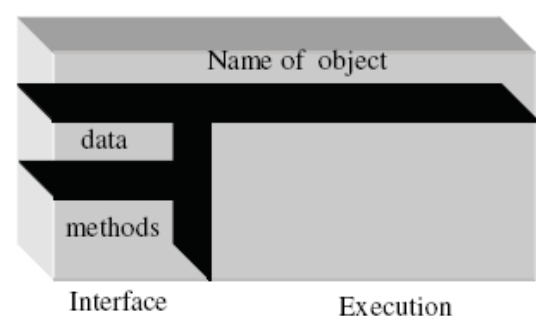


Figure 2.3: Data encapsulation

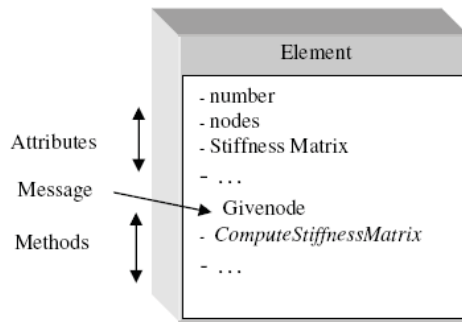


Figure 2.4: Class concept

tail of the operation is left to the object. This “data hiding” is often referred to as encapsulation of the data, behaviour, and state, (see Figure 2.4).

An abstract data type can be specified by the creation of a sub-type or of a subclass which inherits the structures of data and the methods from its ancestor, often called superclass. The mechanism of inheritance can be total as in the Smalltalk language, for which all attributes and methods are inherited by the subclass, but some languages, such as C++ or Java, allow a mechanism of inheritance through the selection of inheritable variables and methods (Gorlen et al 1990; Graham, 1994).

Polymorphism means the ability of objects of different classes to answer the same message in different manners, in other words, the corresponding method can have a different implementation in different classes. As Figure 2.5 indicates, the message “computeStiffnessMatrix” can be addressed to different types of elements and the method

will be different from one type of element to another.

3. RECALL OF REISSNER-MINDLIN PLATE THEORY

Object-Oriented finite element implementation will be illustrated now with the example of a plate element. Shell, beam or continuum elements could be shown alternatively.

We start with a recall; the orthotropic plate formulation for finite elements in bending-shear is based on the theory of Reissner-Mindlin. Their conformity C^0 requires only continuity of w , β_x and β_y (Batoz and Dhett, 1990; Imbert, 1991), where w , β_x and β_y are transverse displacement, rotation of the normal on the middle surface in the (x-z) and (y-z), plans respectively (see Figure 3.1).

We consider isoparametric quadrilateral elements (Dhatt and Touzout, 1984; Batoz and Dhett, 1990; Imbert, 1991). (The approximations of w , β_x and β_y)

$$\begin{aligned} w &= N^T(\xi, \eta) W \\ \beta_x &= N^T(\xi, \eta) \hat{\beta}_x \\ \beta_y &= N^T(\xi, \eta) \hat{\beta}_y \end{aligned} \quad (1)$$

where T denotes transposition.

The strain vector can be expressed as:

$$\{\epsilon\} = \{\{\epsilon_f\}^T, \{\epsilon_c\}^T\}^T = \{Z\{\chi\}^T, \{\gamma\}^T\}^T \quad (2)$$

where $\{\chi\}$ is the curvature vector.

The contribution of bending effect and the contribution of shear effect are respectively:

$$\begin{aligned} \{\epsilon_f\} &= \begin{Bmatrix} \epsilon_{xx} \\ \epsilon_{yy} \\ \gamma_{xy} \end{Bmatrix} = z \{\chi\} = z \begin{Bmatrix} \frac{\partial \beta_x}{\partial x} \\ \frac{\partial \beta_y}{\partial y} \\ \frac{\partial \beta_x}{\partial y} + \frac{\partial \beta_y}{\partial x} \end{Bmatrix} \\ \{\epsilon_c\} &= \{\gamma\} = \begin{Bmatrix} \gamma_{xz} \\ \gamma_{yz} \end{Bmatrix} = \begin{Bmatrix} \beta_x + \frac{\partial w}{\partial x} \\ \beta_y + \frac{\partial w}{\partial y} \end{Bmatrix} \end{aligned} \quad (3)$$

The interpolation functions used are the usual interpolation functions of isoparametric quadrilaterals. In the case of the linear quadrilateral, one gets:

$$\begin{aligned} N^T &= [N_1 \quad N_2 \quad N_3 \quad N_4] \\ N_i(\xi, \eta) &= \frac{1}{4}(1 + \xi \xi_i)(1 + \eta \eta_i) \end{aligned} \quad (4)$$

where ξ or η are taking values (+1) or (-1) according to the consideration of node.

$$W = \begin{Bmatrix} w_1 \\ w_2 \\ w_3 \\ w_4 \end{Bmatrix} \quad \hat{\beta}_x = \begin{Bmatrix} \beta_{x1} \\ \beta_{x2} \\ \beta_{x3} \\ \beta_{x4} \end{Bmatrix} \quad \hat{\beta}_y = \begin{Bmatrix} \beta_{y1} \\ \beta_{y2} \\ \beta_{y3} \\ \beta_{y4} \end{Bmatrix} \quad (5)$$

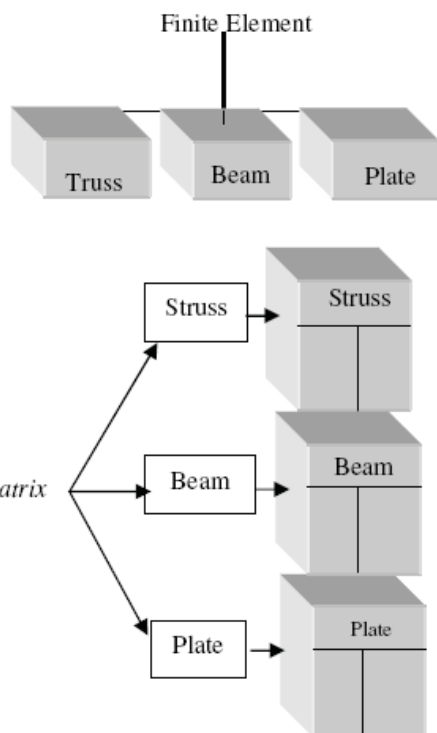


Figure 2.5: Polymorphism

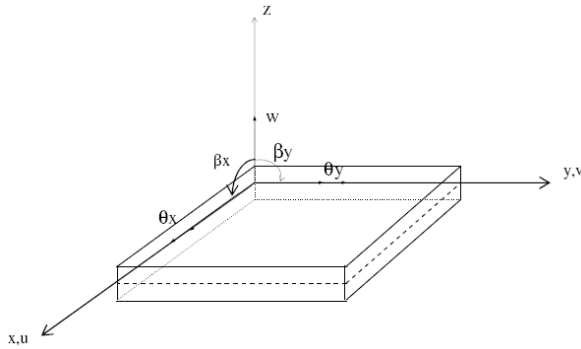


Figure 3.1: Sign conventions for displacements and rotations

By substitution of (4), in the relations of deformations (3), we obtain the bending and shearing deformations matrices of interpolation as follows:

$$\{\chi\} = \{\bar{\epsilon}_f\} = \begin{bmatrix} 0 & \frac{\partial N^T}{\partial x} & 0 \\ 0 & 0 & \frac{\partial N^T}{\partial y} \\ 0 & \frac{\partial N^T}{\partial y} & \frac{\partial N^T}{\partial x} \end{bmatrix} \begin{Bmatrix} W \\ \hat{\beta}_x \\ \hat{\beta}_y \end{Bmatrix} \quad (6)$$

$$\{\epsilon_s\} = \{\gamma\} = \begin{bmatrix} \frac{\partial N^T}{\partial x} & N^T & 0 \\ \frac{\partial N^T}{\partial y} & 0 & N^T \end{bmatrix} \begin{Bmatrix} W \\ \hat{\beta}_x \\ \hat{\beta}_y \end{Bmatrix} \quad (7)$$

$$\text{with } \{\chi\} = \{\bar{\epsilon}_f\} = [\bar{\beta}_f] \{q\} \quad \{\gamma\} = [\beta_s] \{q\} \quad (8)$$

The expression of the deformation energy makes it possible to calculate the stiffness matrix (Batoz and Dhett, 1990), (Imbert, 1991). We have: $U = U_F + U_C$

$$U = \frac{1}{2} \int_{S^e} \{\chi\}^T [D_f] \{\chi\} dx dy + \frac{1}{2} \int_{S^e} \{\gamma\}^T [D_s] \{\gamma\} dx dy \quad (9)$$

$$= \frac{1}{2} \{q\}^T [K] \{q\}$$

$$[D_f] = \frac{h^3}{12} \begin{bmatrix} \frac{E_1}{1-\nu_{21}\nu_{12}} & \frac{E_2\nu_{12}}{1-\nu_{21}\nu_{12}} & 0 \\ \frac{E_2\nu_{12}}{1-\nu_{21}\nu_{12}} & \frac{E_2}{1-\nu_{21}\nu_{12}} & 0 \\ 0 & 0 & G_{12} \end{bmatrix}, [D_s] = hk \begin{bmatrix} G_{13} & 0 \\ 0 & G_{23} \end{bmatrix} \quad (10)$$

where $[D_c] = [D_f] + [D_s]$ is the constitutive matrix, E_1 and E_2 are the Young's moduli in two directions (x) and (y), ν_{12} , ν_{21} are the Poisson's ratios, G_{12} , G_{13} , G_{23} are the shear moduli, and k the coefficient of correction of transverse shear.

Minimization of expression (9), leads to

$$[K] = [K_f] + [K_c] = \int_S [\bar{\beta}_f]^T [D_f] [\bar{\beta}_f] dx dy + \int_S [\beta_s]^T [D_s] [\beta_s] dx dy \quad (11)$$

$$[K] = \int_{-1}^{+1} \int_{-1}^{+1} [\bar{\beta}_f]^T [D_f] [\bar{\beta}_f] \det[J] d\xi d\eta + \int_{-1}^{+1} \int_{-1}^{+1} [\beta_s]^T [D_s] [\beta_s] \det[J] d\xi d\eta \quad (12)$$

where $[J]$ is the Jacobian matrix from the physical to the parent co-

```
Dictionary
Dof
Domain
FemComponent
Element
    PlaneStrain
    Truss2D
    Plate
    Orplate
Load
    BodyLoad
    DeadWeight
    BoundaryCondition
    NodalLoad
LoadTimeFunction
    ConstantFunction
    PeakFunction
Material
Node
TimeIntegrationScheme
    Newmark
    Static
Timestep
FileReader
FloatArray
Column
GaussPoint
IntArray
LinearSystem
    BandSystem
    SkylineSystem
List
Matrix
    FloatMatrix
    BandMatrix
    PolynomialMatrix
Polynomial
    PolynomialXY
Skyline
String
```

Figure 4.1: The C++ finite element class hierarchy

ordinate system. The stiffness matrix $[K]$ is evaluated numerically by selective numerical integration; ($[K_f]$ is integrated with (2x2) Gauss point formula $[K_c]$ is obtained by reduced integration).

The equivalent load vector is written:

$$\{F\}^e = \int_{V^e} [N]^T \{f_v\} dV + \int_{S^e} [N]^T \{f_s\} dS \quad (13)$$

4. IMPLEMENTATION INTO FEMOBJECT CODE

The enrichment of FEMObject code was carried out so that the concept of object was preserved by leaving the existing methods

```
FloatMatrix* Plate::computeStiffnessMatrix() {
    this->computeStiffnessMatrixB();
    this->computeStiffnessMatrixS();
    stiffnessMatrix = stiffnessMatrix->GiveCopy();
    stiffnessMatrix->plus(stiffnessMatrixS);

    return stiffnessMatrix;
}
```

Listing 1: Creation of a new class: plate type element

```
Element* Element::ofType(char* aClass) {
    Element* newElement;
    if(!strcmp(aClass, "Pl", 2))
        newElement = new Plate(number, domain);
    else if(!strcmp(aClass, "Or", 2))
        newElement = new Orplate(number, domain);
    else {
        printf("%s: Unknown element type\n", aClass);
        exit(0);
    }

    return newElement;
}
```

Listing 2: Implementation of the computeStiffnessMatrix method

Tasks	Attributes	Methods
1) Creation	stiffnessMatrixS	new class
2) Computations a) Interpolation matrices b) Constitutive matrix	- constitutiveMatrixS	computeNMatrixAt:aGaussPoint computeBMatrixAtB:aGaussPoint computeBMatrixAtS:aGaussPoint computeConstitutiveMatrixB computeConstitutiveMatrixS
2) Numerical integration a) Gauss point b) Jacobian c) Weight	- jacobianMatrix -	computeGaussPoints giveJacobianMatrix computeJacobianMatrix computeVolumeAround

Table 1: Task list of class Plate and Orplate

unchanged and creating a new class “Plate” inheriting the methods of the former base “Element” class, and re-implementing (polymorphism) some of them.

Starting from the existing class hierarchy a new subclass of class “Element” called “plate” is introduced in Figure 4.1. One of the principal classes in FEMObject is the Element class which allows to calculate all the characteristics of an element. By adding the plate class, it was found meaningful to split the stiffness matrix into two, one due to shearing and the other due to bending. Once these two matrices are calculated the stiffness matrix of the element is assembled from the two contributions (bending and shearing).

In order to create a new class of plate type Element we proceed as follows (see Listing1).

In the class Element of FEMOBJ, a method ComputeStiffnessMatrix calls three other methods : ComputeBmatrix (for the calculation the shape functions derivative); computeConstitutiveMatrix (for the calculation of the constitutive matrix), and computeVolumeAround (to calculate the Jacobian). This last method remains unchanged because the Jacobian is identical for all types of 4-node quadrilateral isoparametric elements. On the other hand, the other existing methods must be modified, because of the need to compute the shearing and bending contributions.

The unchanged method computeVolumeAround is inherited from the base class Element, whose implementation will be required for the computation of the Jacobian for the plate element.

On the other hand, the computeStiffnessMatrix method implemented in Element is overridden by another implementation in class Plate and Orplate.

The plate class has to implement a computeStiffnessMatrix; this new method now makes use of the new methods computeStiffnessMatrixB and computeStiffnessMatrixS and sums the results to obtain the correct stiffness matrix (see Listing 2).

On the level of these two methods one can create the elementary matrices. The computeStiffnessMatrixB method uses computeBmatrixB (which calculates the bending matrix form the discretized symmetric gradient operator) and computeConstitutiveMatrixB (which calculates the bending constitutive matrix). Similarly, method computeStiffnessMatrixS computes the shearing contribution to the stiffness matrix.

The implementation is sketched in Figure 4.2 and detailed in appendix A1, the task list of both classes Plate and Orplate is given in Table 1.

Remarkably, notice that that all changes in the existing code remain concentrated in only two classes Plate and Orplate, while the rest of the code remains untouched (see Figure 4.1).

5. APPLICATION

This article aims at showing the effectiveness of Object-Oriented programming, illustrated by the code FEMObject, when adding a new class which here treats static isotropic and orthotropic plates. To validate the newly developed code we solve now a specific problem.

The numerical validation examples are an isotropic square plate of constant thickness, simply supported and fixed on its four sides, subjected to a centrally concentrated load of intensity F . The geometrical and mechanical data of the structure are given in Figures 5.1 and 5.3, as well as the boundary conditions which are imposed on the boundary of the plate.

In order to study convergence, Figure 5.2 shows the evolution of the normal displacement at the centre of the plate, which is simply supported on its four sides for various grids. Our numerical results are compared with the analytical solution from reference (Batoz and Dhatt, 1990) using the expression:

$$w_{exact} = 0.0116 \frac{Fa^2}{D}$$

Figure 5.4 represents the evolution of the value of the normal dis-

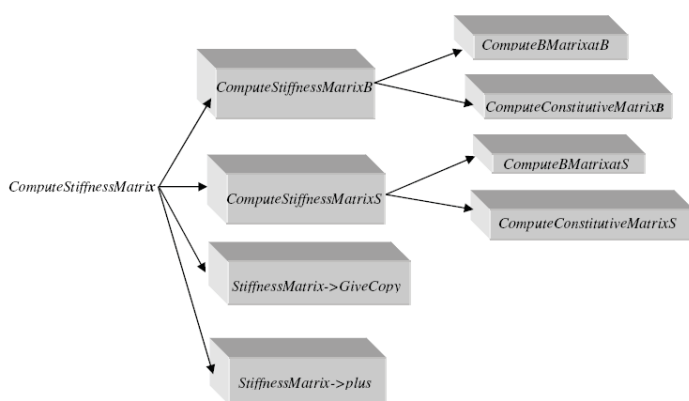


Figure 4.2: Example of an added class methods

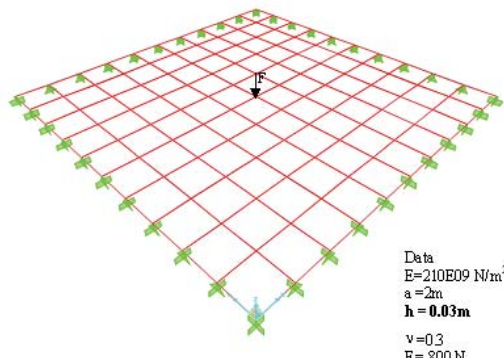


Figure 5.1: Isotropic square plate simply supported on its four sides subjected to a concentrated load F

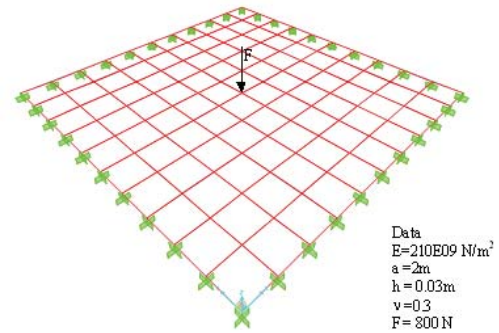


Figure 5.2: Isotropic square plate clamped on its four sides under concentrated load F

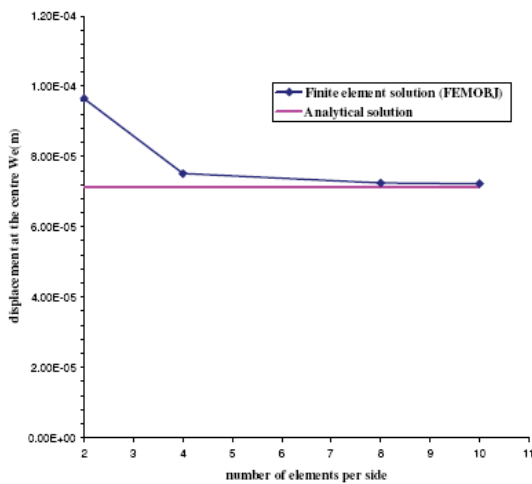


Figure 5.2: Convergence of finite element solution for different mesh refinements for a simply supported isotropic plate

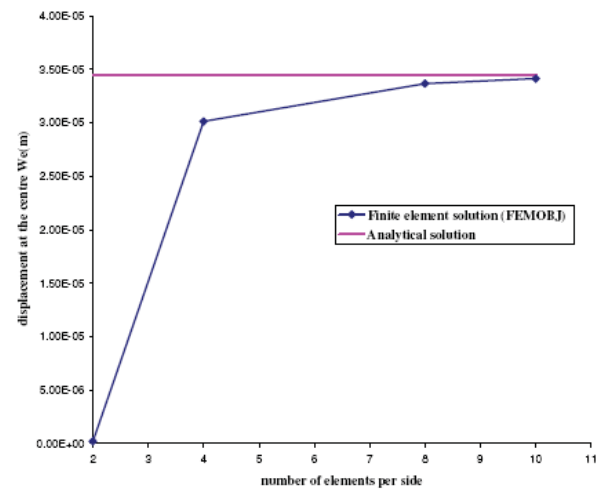


Figure 5.4: Convergence of finite element solution for different mesh refinements for an isotropic plate embedded on its four opposite sides

placement at the centre of the clamped plate on its four sides for various grids. Our numerical results are compared with the analytical solution given in (Batoz and Dhatt, 1990) using the formula:

$$w_{exact} = 0.0056 \frac{Fa^2}{D}$$

Starting from a grid of 8x8 elements, convergence is satisfactory for these two examples; the relative error with 8x8 grid is 1.3% for the first example and 1.2 % for the second one.

The structures represented in Figures 5.5 and 5.7 are orthotropic thin plates of constant thickness, simply supported for the first one and clamped on the four sides for the second, and subjected to a constant load of intensity F applied at the centre of the plate. The geometry, material data, and boundary conditions of the two structures are given in Figures 5.5 and 5.7. Figures 5.6 and 5.8 show the comparison of the numerical results for the deflection along the two semi-axes of symmetry of the simply supported orthotropic plate and the evolution of the value of the normal displacement of an orthotropic fixed plate for different grids with those from the analytical solution given in (Shi and Bezzine, 1988) respectively:

$$w_{exact} = 0.3084 \times 10^{-2} \frac{Fa^2}{D_{22}} = K \frac{Fa^2}{D_{22}} \times 10^{-2}$$

$$w_{exact} = 1.17180 \times 10^{-3} \frac{Fa^2}{D_{22}}$$

In Figure 5.6 one sees clearly that the behaviour of the orthotropic plate is different along the two axes x and y , as expected. The convergence in Figure 5.8 is satisfactory starting from an 8x8 grid; the relative error for the 8x8 grid is 2.6%.

6. CONCLUSION

Through the example of the addition of a plate element in existing C++ code, FEMObject, this paper has shown how Object-Oriented programming makes it possible to easily develop new features in finite element codes, showing such Object-Oriented programs to be more modular, reusable and more easily expandable.

The Object-Oriented approach is shown to offer undeniable advantages compared to earlier programming structures. The encapsulation of the data largely improves the modularity, and thus the reliability and legibility of the code are increased. Inheritance allows an automatic reusability of the already developed methods, and polymorphism is a powerful means to raise the level of abstraction. The Object-Oriented approach offers more generic structures, making it possible to overcome a number of difficulties of the traditional implementations of the finite element method.

Object-Oriented Programming also supports the upgrading needs of the finite element method implementation by enhancing modularity and flexibility of evolution. Thanks to the derivation of classes and

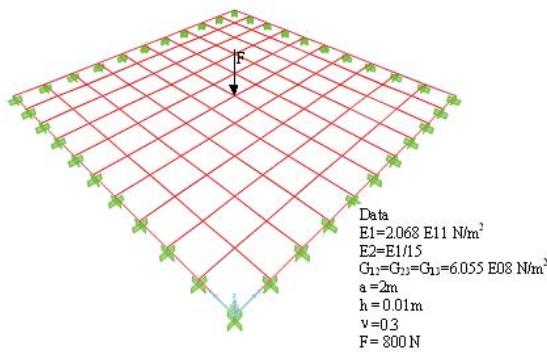


Figure 5.7: Orthotropic square plate embedded on its four sides subjected to a concentrate load F

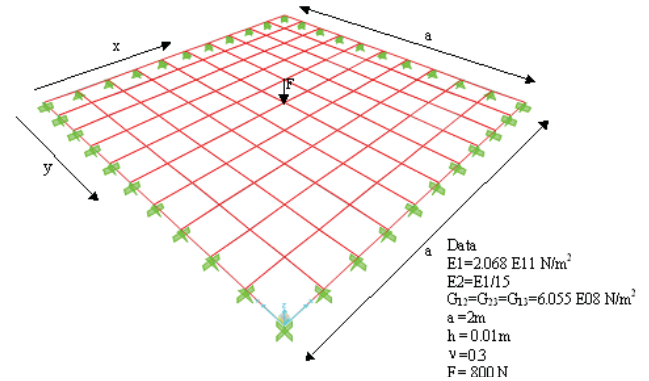


Figure 5.5: Orthotropic square plate simply supported on its four sides subjected to a concentrated load F

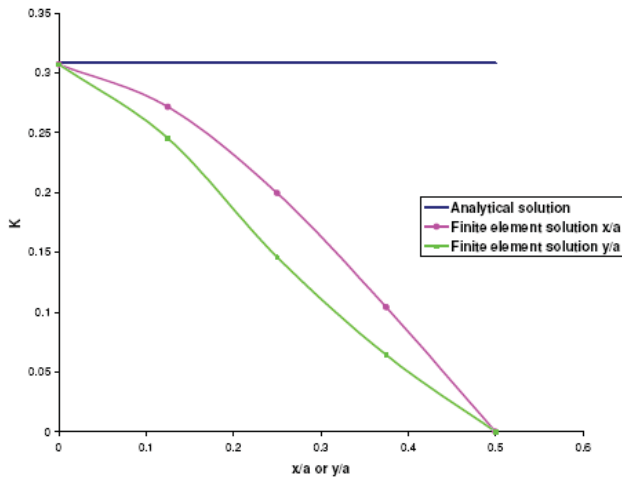


Figure 5.6: Deflection along the two semi-axes of symmetry of an orthotropic plate simply supported with a concentrated load in the middle

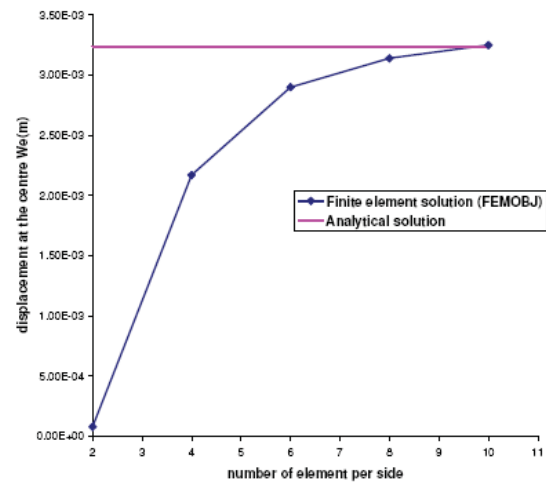


Figure 5.8: Convergence of finite element solution according to the grid for an orthotropic plate embedded on its four opposite sides

a high level of abstraction, Object-Oriented Programming can be an effective tool to keep control of the codes of tomorrow. The late binding capability (polymorphism) facilitates adaptability.

The implementation and numerical testing of a plate element was used to illustrate the argument, but other continuum or structural formulation could have been used as well.

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The full C++ code described in the article can be downloaded from <http://www.ibscientific.net/doi:P0010>

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Placing p53 Back on the Track... The Survival Track?

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ABSTRACT

The tumour-suppressor p53 orchestrates the cellular response to stress conditions through the modulation of signalling pathways involved in both cell-cycle regulation and programmed cell death, apoptosis. The response mediated by p53 prevents the accumulation of genotypic and phenotypic aberrations that ultimately result in loss of cellular integrity. Loss of p53 function is thought to be associated with tumorigenesis. In fact, p53 dysfunction is observed in over 50% of human cancers characterised by lack of differentiation and increased levels of angiogenesis and metastasis. In addition to its putative role in tumour suppression, p53 is also believed to mediate chemo-sensitisation in cancer cells. Therefore, restoring p53 function represents an attractive strategy for cancer therapy. Various approaches have been undertaken to restore p53 function, including p53 gene-replacement therapy, non-genotoxic stimulation of endogenous wild-type p53 and correction of both mRNA and protein products of mutant p53 genes. In this review, the different p53 restoration approaches are discussed in light of the complexity of tumours, the practical challenges facing these restoration strategies, and the yet enigmatic functions of p53 in tumour cells and in sensitisation to anticancer treatments.

1. INTRODUCTION

The p53 tumour-suppressor is a multifunctional protein encoded by the TP53 gene. p53 does not appear to be essential for normal development, however some mutations in TP53 are shown to predispose to tumour formation. In fact, p53 is undetectable under normal conditions, but is activated, stabilised and accumulated - mainly at the post-translational level- in response to various stress signals (e.g. DNA damage, microtubule disruptions, hypoxia and oncogene activation), whereby it governs cell growth and cell death decisions. Subsequently, p53 engages in a plethora of protein-protein and protein-DNA interactions, and regulates the expression of over 100 genes (Xu et al., 2001), resulting in various cellular responses including cell cycle arrest, senescence, differentiation, DNA repair, inhibition of angiogenesis, and apoptosis.

Accordingly, inactivation of p53 can result in impaired cellular responses to stress conditions, allowing cells with genetic and cellular aberrations to survive (Lane, 1992; and Levine, 1997). This is strongly underscored by the tumour predisposition in p53^{-/-} knock-out mice (Donehower et al., 1992) and in Li-Fraumeni Syndrome patients, who have inherited mutations in TP53, as well as the observation that loss of p53 in tumour cells can hamper the apoptotic effect of some chemotherapeutic agents (Lowe et al., 1993; and Levine, 1997).

Loss/mutation of p53 has been reported in a wide range of cancers including lung (70%), colon, head & neck (60%), and stomach cancers (45%)¹. While p53 mutations occur early in some cancers such as melanomas, p53 is mutated at later stages in other cancers (e.g. colorectal cancer) probably after the inactivation of additional genes. This suggests that in addition to the abrogation of normal p53 activity, mutant p53 may also display an oncogenic-like gain of function by giving transformed cells a survival advantage (Sigal and Rotter,

2000). Cancer cells with wild-type p53 (wt p53) often have alternative aberrations in the p53 pathway; these include over-expression of negative regulators of p53 (Watanabe et al., 1996), and mutations in upstream kinases (Lozano, 2005). Additionally, cancers with intact upstream and downstream p53 pathways can be subject to wt p53 inactivation through other mechanisms such as the promotion of its degradation by the human papilloma virus (HPV) oncoprotein E6 observed in 90% of cervical cancers, and its abnormal cytoplasmic localisation in neuroblastomas (Thomas et al., 1999; and Moll et al., 1999). With all of this in mind, restoring p53 functions in tumours would, in theory, represent a potential target for cancer therapy. Herein, strategies that have been employed to restore or induce p53 functions are reviewed, and some of the practical and theoretical obstacles facing different approaches are discussed.

2. P53 GENE REPLACEMENT THERAPY

One of the pioneer strategies aiming to restore the function of vital genes for therapeutic ends is gene therapy. Gene therapy using viral delivery systems has been employed in an attempt to transfer wt p53 into cancer cells. Ideally, the viral delivery of a small number of p53 transgenes would result in bystander outcomes in the tumour bulk due to anti-angiogenic effects, the cytotoxic immune responses, and the spread of viral particles containing the therapeutic gene (Frank et al., 1998; and Nishizaki et al., 1999). The activity of the introduced p53 may be higher in transformed cells than in non-transformed

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¹ From p53 database on: http://p53.free.fr/Database/Mutation_Analysis/p53_databaseANAL.html

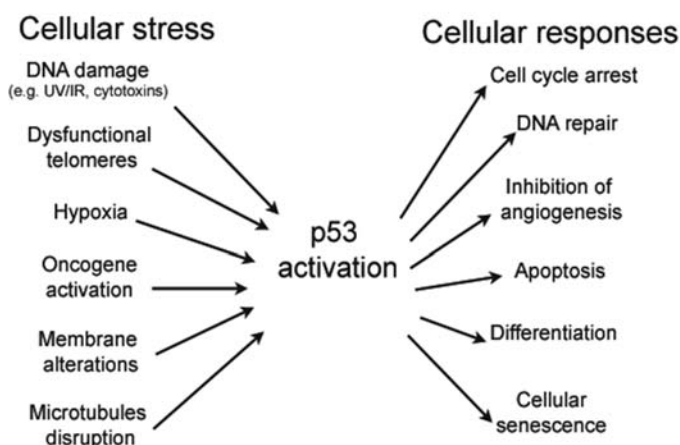


Figure 1: p53 activation and cellular responses

counterparts as a result of oncogene activation (an inducer of p53, see Figure1), potentially leading to selective targeting (D'Orazi et al., 2000). In fact, adenoviral constructs expressing wt p53 resulted in tumour regression and apoptosis in various human tumour xenograft models (Neyns et al., 2003; Nielsen et al., 1997; and Kock et al., 1996). p53 gene transfer also sensitised tumour xenograft models and some cell lines to chemotherapeutic agents (YU et al., 2004; Khuri et al., 2000; Nguyen et al., 1996; Gurnani et al., 1999; and Ganjavi et al., 2005). Following these successes and some promising phase I/II clinical trials, several other trials were undertaken (Edelman et al., 2003; and Alavi et al., 2001), but the p53 gene therapy approach failed in many of these clinical trials (Zeinmet and Mrth, 2003; and McNeish et al., 2004). In ovarian cancer, for instance, not only did p53 transfer fail to improve the effectiveness of chemotherapy, but it was also associated with increased toxicity. Time will tell whether the ongoing phase III clinical trials will be as disappointing. This however, raises a very important question: why then were the pre-clinical studies so encouraging? There are several lines of explanation; firstly it is questionable whether human tumour xenograft models in mice, in which p53 gene therapy was proven effective, mimic the biology, heterogeneity, and genetic instability of tumours as well as the possible presence of stem cell-like cancer cells in patients. Secondly, the immune response to viruses can limit the effectiveness of the treatment (a general limitation of gene therapy) by producing neutralising antibodies, hence attenuating p53 expression (Stallwood et al., 2000; and Oin et al., 1997). Administering the transgene repeatedly with different serotypes could bypass this specific problem (Marck et al., 1997). Alternatively, non-viral systems e.g. naked DNA and cationic liposomes could be better and safer tools for gene delivery. Using liposomes, the delivery of large amounts of transgenes and multiple administrations are also possible (Willis et al., 2002).

Another important drawback is the fact that some cells are more sensitive to p53 activity (e.g. the gut epithelium and haematocytes), and thus devising selective targeting approaches is a major objective. This could be achieved by ablating natural viral tropism to spare normal cells (Jakubzak et al., 2001) or introducing novel tropism to specifically target tumour cells, by conjugating adenoviral vectors with ligands/antibodies to receptors abundantly expressed on tumour cells (Douglas et al., 1996; and Kelly et al., 2000). p53 delivery using conditionally-replicative adenoviruses has also shown promising results, despite claims that the expression of exogenous p53 may compromise the main goal of viral replication (Haviv et al., 2002; Georger

et al. 2002; Pistors et al., 2004; Georger et al., 2005; and O'Shea et al., 2004).

In addition to the practical obstacles discussed above, there are also some theoretical issues. Over-expression of p53 can lead to premature aging (Tyner et al., 2002; and Dumble et al., 2004) and thus, the expression of p53 transgenes should be tuned by adding, for instance, transcription-control regions on the delivery system (Ring et al., 1997). Additionally, the introduced wt p53 can be inactivated by the endogenous mutant p53 through oligomerisation, resulting in a dominant negative effect (Milner et al., 1991; and Chene et al. 1998). Though, some argue that this concern is unfounded since wt p53 is phenotypically dominant to mutant p53 when present in equal ratios (Frebourg et al., 1994) and the deletion of the second p53 wt-allele is generally needed for the development of many tumours.

3. RESTORING THE TUMOUR-SUPPRESSING FUNCTION OF MUTANT p53

Ninety five percent of p53 mutations are located in the DNA binding domain (DBD), and 76.6% of which are point mutations resulting in single amino-acid substitutions². The frequent occurrence of these mutations during tumour development suggests that these mutants may provide survival advantages. In addition to possible interference with wt p53 function by dominant repression, mutant p53 may counteract the normal function of p53 by inhibiting the induction of apoptosis and activating the expression of growth-promoting genes, resulting in uncontrolled proliferation and genetic instability (Koonin et al., 2005; Cadwell et al., 2005; and Ohiro et al., 2003). (Figure 2).

Structural and biophysical studies showed that the common effects of most of p53 mutations are the destabilisation of the protein at physiological temperature, and/or disruption of normal p53-DNA contacts (Bullock et al., 1997; and Friedlander et al., 1996). Therefore, restoring normal protein-protein and protein-DNA interactions of the mutant p53, by stabilising the active conformation represents an attractive approach (Seemann et al., 2004). This strategy would simply rescue the endogenous p53, and specifically target improperly folded mutant p53. It also exploits the high levels of mutant p53 and its possible activation in tumour cells due to stress signals, signals that are absent in normal cells.

Conformational changes were first shown to be reversible when an antibody, recognising the extreme C-terminus of p53, was found to restore the activity of mutant p53 (Abarzua et al., 1995). This C-terminal domain is a negative regulator of p53-DNA interaction, and thus neutralising its effect could, in theory, recover the high affinity binding of p53 to DNA. Accordingly, single-chain antibody fragments (scFv) have been derived from monoclonal antibodies to p53 C-terminus (Caron de Fromentel et al., 1999).

Additionally, small peptides have been employed to stabilise the folding of p53 DBD. CDB3, which was derived from the crystal structure of ASPP-p53 complex, was proven to bind and efficiently rescue two p53 hot spot mutants in vivo (Friedler A et al., 2002; Is-saeva N et al., 2003). A small chemical, CP-31398, was also shown to suppress tumour growth in xenograft models (Foster et al., 1999). However, biophysical and in vivo experiments failed to detect any binding of CP-31398 to p53 DBD or restoration of p53 function at non-toxic concentrations (Rippin et al., 2002; and Tanner et al., 2004). The mechanism of action of CP-31398 is therefore unclear.

² See p53 database on <http://www-p53.iarc.fr/index.html> and also <http://p53.free.fr/>.

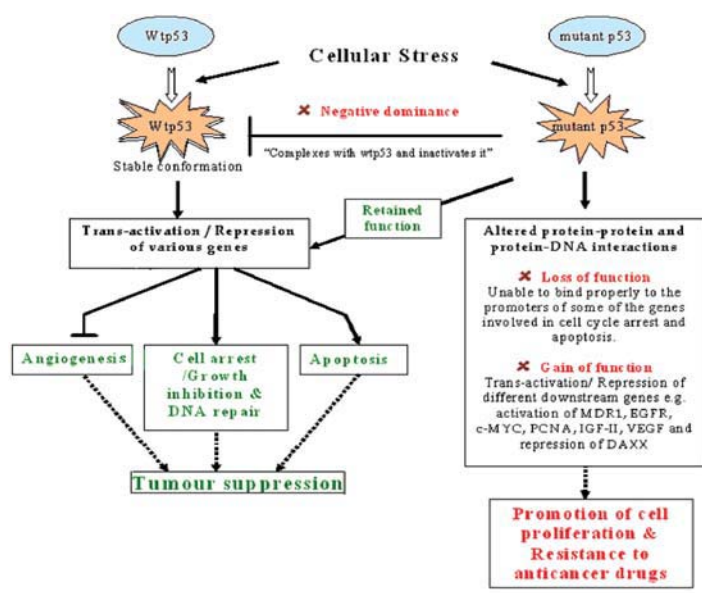


Figure 2: Wild type and mutant p53 in response to cellular stress. The functions of wild type and mutant p53 are compared in this diagram. Some of the downstream genes trans-activated / repressed by mutant p53 are mentioned in the diagram

The efficacy of HSP90 inhibitors (e.g. geldanamycin) in cancer therapy and chemosensitisation is also of interest. Besides inducing the degradation of mutant p53 (via p53-Mdm2 dissociation from HSP90), these compounds abolish the reactivation of temperature-sensitive mutants. Since HSP90 chaperone is not required for wt p53 stabilisation, developing potent antagonists may prove effective (Muller et al., 2004). Glycerol, a chemical chaperone, was also found to restore the normal function of mutant p53, induce apoptosis and enhance the radio-sensitivity of p53-defective tumour cells (Ohnishi et al., 2000; Ohsini et al., 2002; and Yuki et al., 2004). Probably the most promising compound is PRIMA1 (p53 Reactivation and Induction of Massive Apoptosis), which was isolated from the NCI³ chemical library (Bukov et al., 2002). This molecule leads to apoptosis only in p53-defective cells and corrects the DNA binding properties of many p53 mutants in vitro. Its anti-tumoural activity and non-toxicity were confirmed in human tumour xenograft in mice. This molecule has also anti-angiogenic effects (Liang et al., 2005) and can activate p53-induced transcription-independent apoptosis (Chipuk et al., 2003). Although these approaches seem promising, they still own some practical limitations. For example, therapeutic peptides, which are potentially specific and non-toxic, can be degraded and quickly eliminated by the immune system. Also, for small molecules drug resistance can still arise (Fojo, 2002).

A more elegant approach is the trans-splicing ribozymes, which can correct mutant mRNA directly by exchanging mutant p53 RNAs with wt p53 RNA sequences attached to their 3' end (Bagheri et al., 2004). Such ribozymes were shown to increase the expression of p21 (a cell cycle inhibitor) and Bax (a pro-apoptotic gene) and efficiently induce apoptosis in transfected human cancer cells (Watanabe et al., 2000). This strategy corrects the fault from its roots and triggers expression of wt p53 only in cells with mutant p53 mRNA. Compared to gene therapy and corrections of p53 protein, mRNA repair avoids possible uncontrolled up-regulation, gain of function and negative-

dominant effects of p53. Thus, one would think that mRNA repair is the very promising method. Unfortunately, efficient and non-immunogenic delivery of ribozymes remains a big challenge (Wang et al., 2003).

4. NON-GENOTOXIC STIMULATION OF ENDOGENOUS WT p53; LESSONS FROM p53 REGULATION

Many cancer cells that retain their wt p53 have defects in either activating or responding to p53. For example, over-expression of the negative regulator MDM2, or loss of the stabilising protein p14ARF are frequent in many tumours. One would hope that stabilising or activating wt p53 in tumour cells would induce an apoptotic response. The increasing knowledge of p53 regulation has facilitated the development of various non-genotoxic methods for wt p53 stimulation. Some of these are summarised in Table 1.

One strategy aims at stabilising p53 by disrupting its interaction with negative regulators such as MDM2 and iASPP. Depleting or inhibiting negative regulators e.g. CRM1 and COP1 is another way to achieve p53 stabilisation. No specific drug has been designed so far to mimic or induce the activity of some p53 activators like p14ARF, HAUSP and Ref-1, which are nonetheless attractive candidates for cancer therapy. Undoubtedly, with the expanding knowledge of p53 regulation, further targets will continue to emerge. However, non-genotoxic stimulation of p53 can have some limitations. First, the use of peptide therapies as mentioned above is dependent on finding efficient ways of delivery and is limited by their quick elimination. In addition, some molecules are not selective and can produce severe side effects in non-tumour cells.

5. HEADING IN THE RIGHT DIRECTION?

Adding to the practical challenges facing each technique, important general issues have yet to be resolved. First, the cellular response to p53 reactivation may vary. For example, cell lines treated with CP-31398 were shown to undergo either cell cycle arrest or apoptosis, with cell cycle arrest preceding apoptosis in some cases (Takimoto et al., 2002). While previous reports suggested that PRIMA-1 induced only growth suppression in vivo (Fojo, 2002), later studies demonstrated the reactivation of p53 by this compound, the activation of some p53 downstream genes, and the subsequent induction of apoptosis in p53-defective cells (Bykov et al., 2002). One model suggests that p53 has higher affinity for the promoters of cell cycle arrest genes, an affinity that can change in response to cellular stress. Under such conditions, p53 accumulation, modification and interaction with specific cofactors enable it to trans-activate pro-apoptotic genes (Vousden et al., 2002). This is supported by the dependence of p53 activation outcome on p53 levels in vitro and the ability of some low-affinity mutants to induce only cell cycle-arrest. However, p21 is poorly induced in some experimental models and the basal levels of p53 in some cells can be higher than the stimulated levels in other cells (Fojo, 2002).

Alternatively, it has been suggested that the activation of few genes including p21 is sufficient to achieve cell cycle-arrest, whereas several factors with putative pro-apoptotic function are necessary but not exclusively sufficient to induce apoptosis. Nevertheless, no definite correlation has yet been established between promoter binding and apoptosis induction (Kaeser et al., 2002). Some genotoxic agents can kill cells harbouring mutant p53 that cannot trans-activate pro-

³ US National Cancer Institute (NCI) drug discovery program. For more information see <http://dtp.nci.nih.gov>.

Target	Therapeutics	Mechanism	Reports
Negative regulators: MDM2 MDM2/Parc/ iASPP/p300	Nutlins. RITA.	MDM2 antagonists. Induction of an active conformation of p53?	Blocks p53 binding to MDM2 and control tumour growth in xenograft models (Vassilev et al., 2004). Restores apoptosis-inducing function of p53 selectively in tumour cells (Issaeva et al., 2004).
COP1 Targets p53 for degradation in an ubiquitin-dependent fashion, independent of MDM2. Over-expressed in some cancers.	Small interfering RNA (siRNA). Small molecules?	Depletion of COP1 Inhibitors of COP1	Stabilisation of p53 in vitro (Dornan et al., 2004). -
CRM1 Nuclear exporting	LMB.	Inhibition of CRM1 prevents p53 export and degradation.	Normal cells recover from p53-induced cell cycle-arrest but tumour cells undergo apoptosis (Smart et al., 1999). But there are reports that p53 can be ubiquitinated even in the nucleus as well (Inoue et al., 2001).
HAUSP Rescues p53 from degradation by deubiquitinating it (Yang et al., 2004).	Design HAUSP derived peptides.	Stabilisation of p53.	-
p14^{ARF} Prevents nuclear export of p53 by inhibiting the E3 ligase activity of MDM2.	Design p14 ^{ARF} derived peptides.	Stabilisation of p53.	-
Ref-1 Activates p53. (Meplan et al., 2000; Hainaut et al., 2001; Gainddon et al., 1999; and Hanson et al., 2005).	Inducing it or derive or design of molecules that mimic its function?	Activation of p53.	-

Table.1: Different targets for the non-genotoxic stimulation of endogenous wt p53. Potential targets for cancer therapy emerge quickly with the increasing knowledge of p53 regulation. Here some strategies are shown. p14^{ARF}: product of the alternative reading frame of the INK4a gene. iASPP: inhibitory member of the ASPP family. MDM2: human/mouse double minute protein; a negative regulator of p53. LMB: leptomycinB, an antibiotic. COP1: constitutively photomorphogenic 1. HAUSP: Herpes-associated ubiquitin specific protease. Ref-1: Redox factor-1.

apoptotic genes (Bottini et al., 2000), suggesting the existence of transcription-independent apoptosis. It is also possible that p53 is not the only critical player in the life/death story (Liu et al., 2002). While some argue that apoptosis is the most conserved function of p53 (Slee et al., 2004), others suggest that apoptosis is probably just an auxiliary function of p53 which over-rides cell cycle-arrest under specific conditions (Fojo et al., 2002). In this context, the decision may depend more on the cellular context and the type of damage.

The role of p53 in sensitisation to anticancer therapies is another controversial topic. Loss/mutation of p53 often associates with chemoresistance and relapse in leukaemia, Wilms' tumours and testicular cancers, and correlates with poor prognosis in breast, lung, colorectal, head & neck cancers. In other cancers, p53 status associates poorly with chemosensitivity (Brown et al., 1999; and Viktorsen et al., 2005). Conversely, an association between p53 mutation and good prognosis was revealed in some brain tumours (Rout et al., 2002) and p53 disruption in p53-knockout mice was shown to result in an enhanced rather than decreased sensitivity to irradiation (Weller, 1998). Can these conflicting and confusing reports be reconciled?

In fact, chemosensitivity may depend on cell type and drug specificity. For instance, p53 sensitises human tumour xenografts specifically to Mitomycin-C (Koike et al., 2004). Additionally, the interpretation can be difficult in some solid tumours e.g. malignant gliomas where some tumours said to have mutant p53 can harbour wt p53 subpopulations. Clinical results can also be obscured by the highly heterogeneous population of p53 mutants (different properties and functions) (Soussi et al., 2005). Furthermore, immunohistochemical detection of p53, often used as a substitute for the identification of mutant genes, has imperfect sensitivity and specificity. Besides, many cancer cells don't need p53 for chemotherapy-induced cell death (Blagosklonny, 2001). In this context, poor correlation would not be

too surprising, supporting recent suggestions that p53 status is not sufficient in predicting chemosensitivity (Koike et al., 2004).

Another important issue is that p53-defective tumour cells are likely to suffer from other impairments. Defects in the expression or regulation of apoptotic factors such as Bax and caspases will prevent p53 from accomplishing its apoptotic function. These aberrations could be of genetic and/or epigenetic nature, adding a new dimension to the complication (Wolf et al., 2001; Baylin et al., 2000; and Feinberg et al., 2004). Finally, it can be argued that chromosomal instability is irreversible and so restoring p53 will not help. There is no evidence for the importance of p53 in established tumours where the malignant phenotype persists after introducing p53. In malignant lymphomas for example, p53 mutations affect overall survival in low-risk but not in high-risk patients which may suggest that the latter group has accumulated additional genomic instabilities rendering p53 dysfunction less important (Moller et al., 1999). However, p53 is undoubtedly important in the development of tumours, and thus restoring p53 in earlier stages of cancer can be beneficial. (Sigal and Rotter, 2000)

6. RESTORING p53 INSIDE CANCER FORTRESSES: ANY USE THEN?

Intensive studies on the regulation of p53, its function and structure, its protein and DNA interactions, have inspired therapeutic approaches aiming to restore p53 function in cancer cells. These approaches range from gene therapy and repair of mutant p53 transcript to rescue of mutant p53 protein and non-genotoxic stimulation of wt p53. However, these strategies are based on two controversial roles of p53; its importance in chemosensitisation and in suppressing the malignant phenotype. Furthermore, cancer arises from myriad com-

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binations of genetic and epigenetic abnormalities and thus multi-gene repair would be, in theory, the only efficient therapeutic strategy. In this context, one route would involve the use of replication-selective oncolytic viruses to deliver multi-vector systems armed with strong anti-tumoural genes e.g. suicide genes (e.g. CytochromeC, caspases). Therefore, we are experiencing a shift from the magic bullet dream to the more realistic multi-target therapeutic approach.

The concept of cancer stem cells adds another dimension to the problem. The possible presence of a reservoir of proliferating, undifferentiated, tumour-prone stem cells is sufficient to cause recurrence even after successful remissions (Bonnet, 2005; and Huntly et al., 2005). So, is restoring p53 unlikely to be effective?

I believe that a fuller understanding of the complex cellular and molecular biology of cancers is the way forward. By achieving a comprehensive picture of various networks, one would hope that it would lead to design therapies that are effective in at least some types of cancers, and yet target just a limited number of key pathways, one of which could be the p53 pathway. Therefore, p53 restoration methods certainly deserve further investigation.

Many of the novel therapies discussed here though are limited by current technology for delivering the therapeutic agent (virus, gene, liposome, ribozyme, small molecules) selectively to cancer cells, which are likely to be widely dispersed in the patient. New ideas are emerging rapidly to overcome these practical difficulties (Xu et al., 2002; and Yu et al., 2004). p53 gene therapy suffers from the same drawbacks as any other gene replacement therapy but has also its specific theoretical limitations. Therefore, The design of genetically engineered p53 with increased anti-tumoural activity may yield more efficient p53 gene therapy, by producing for instance p53 variants with increased affinity for promoters of pro-apoptotic genes, and which are resistant to inactivation by negative domination and degradation.

Different strategies might not have to compete but rather combine. Testing the simultaneous administration of several therapeutic strategies such as combining p53 stabilising agents with p53 mRNA repair might be possible in the near future. However, targeting p53 alone might not be sufficient to achieve significant, long lasting effects, so combining it with other cancer therapies might prove useful. In this context, restoring p53 function should at least be effective in sensitising a subset of cancers that are known to be pro-apoptotic e.g. leukaemia and testicular cancers (Fojo, 2002).

Paradoxically, inhibition of p53 seems to sensitise resistant cells to cytotoxins in cancers like astrocytic gliomas, where cell cycle-arrest is the principle outcome of p53 activation (Xu et al., 2005). This finding comes as devastation to the well documented role of p53 activation. Therefore, both activation and inactivation of p53 are considered in cancer therapy, highlighting the importance of this protein and its intermingled tasks. By mastering the complexity of p53 pathways, the regulation and functions of both wt p53 and mutant p53, and finally a more detailed characterisation of different tumour types, it will hopefully be possible to devise tumour-specific therapies. However, these intensive investigations into different pathways should be paralleled with the study, characterisation and targeting of putative cancer stem cells.

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